In-silico Study of the Developed Hydroxychloroquine-based ACE2 Inhibitor Molecules Against COVID-19: Molecular Modeling and Docking

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Abstract-In the present study, we will verify the action of hydroxychloroquine-based derivatives on ACE2 which is considered to be the main portal of entry of the SARS-CoV-2 virus and constitutes an exciting target given its relative genetic stability compared to viral proteins. Thus, 81 molecules derived from hydroxychloroquine by substitutions at 4 different positions were generated in-silico and then studied for their affinity for ACE2 by molecular docking. Only 4 molecules were retained because of their affinity and bioavailability demonstrated by molecular dynamics and molecular docking calculations using COSMOtherm and Materials Studio software.

Keywords-hydroxychloroquine; molecular modeling; Covid-19; ACE2; affinity

I. INTRODUCTION

Covid-19 is caused by SARS-CoV-2 [1] which is one of the emerging respiratory viruses, including MERS (Middle East Respiratory Syndrome) and SARS-CoV (Severe Acute Respiratory Syndrome), which all belong to the same family of coronaviridae [2]. The most common symptoms include fever, dry cough, muscle fatigue, headache, and diarrhea in some cases. Discovered in Wuhan in China in December 2019, this disease quickly spread throughout the world [3]. A few months after the start of the pandemic, more than 2,500,000 people have already died, and more than 100 million have been infected. To date, there is no effective cure against Covid-19 [4] and it is necessary to wait several months before the use of vaccines reaches a satisfactory level. During this time, the treatment of the disease relies on drugs to relieve the severe symptoms of the disease. To this end, more than 200 drugs have already been the subject of clinical trials, including hydroxychloroquine [5].

By targeting the SARS-CoV2 virus, it has been shown that chloroquine and several of its derivatives can bind to several viral proteins [6, 7]. Besides, chloroquine and its derivatives can also bind to ACE2 [8, 9]. The choice of this target is based on two main facts: the first is that ACE2 is the main entry point for the virus and the second is because of its genetic stability

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[10, 11]. Chloroquine and hydroxychloroquine have been the subjects of several studies to explain their effect on the SARS-CoV2 virus proteins [12, 13] such as NSP3, main protease, RNA dependent polymerase, spike glycoprotein, ADP-ribose-1 monophosphatase, and NSP9 replicase protein [6] These interactions, determined in silico, mean that chloroquine and its derivatives are potential active molecules against SARS-Cov2 [14, 15]. It appears -in many studies- that hydroxychloroquine interacts with ACE2 (PBD code: 6M18) [8].

We performed the present work to study, in silico, the effect of a series of hydroxychloroquine-derived molecules on ACE2. Thus, 81 molecules were obtained by substitution of hydroxychloroquine on 4 different positions. The study aims to estimate the affinity of the selected molecules for ACE2, the prediction of their bioactivity, molecular docking, and their electronic properties by COSMO-RS using COSMOtherm software (version 15.0). The second part of this work is focused on the selection of the preferred molecules according to their physicochemical properties calculated by molecular modeling and molecular docking method using Materials Studio software (version 17.1).

II. MATERIALS AND METHODS

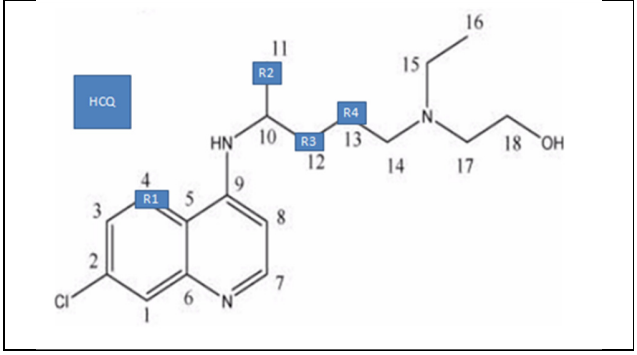
The chemical properties of hydroxychloroquine were calculated using SwissADME (Table I). Four positions, 4, 11, 12, and 13, were chosen to undergo modifications by substituting the original chemical groups with others (Table II).

TABLE I. HYDROXYCHLOROQUINE PROPERTIES CALCULATED BY SWISSADME

Properties	Values
Molecular weight	335.9g/mol
XLogP	3.6
Hydrogen acceptors	4
Hydrogen donors	2
Rotative bonds	9
Exact mass	335.17644g/mol
Mono-isotopic mass	335.17644g/mol
TPSA (Topological polar surface area)	48.4A^2
Heavy atoms	23

TABLE II. CHEMICAL GROUPS SELECTED TO CREATE NEW MOLECULES.

Position	Original	First modification	Second modification
4 – R1	H	CH_3	F
11 – R2	CH_3	CH_2OH	CHO (aldehyde)
12 – R3	CH_2	CH-NH_2	CH-CH_3
13 – R4	CH_2	-O-	CH_2OH



It should be noted that only these 4 positions leave the interaction between the candidate molecules with the receptor site relatively stable. These substitutions made it possible to generate 81 new molecules, which were subjected to the study of their affinity for ACE2 by examining two essential parameters: Ligand Efficiency (LE) and Lipophilic Ligand Efficiency (LLE). Molinspiration Chemoinformatics software carried out the prediction of the bioactivity of the selected molecules. This step allows classifying the molecules according to their capacity to bind to the protein. The study on the protein ACE2-ligand complexes was investigated using SeeSAR software. In the last step, we studied the electronic properties of these molecules by COSMO-RS software.

III. RESULTS AND DISCUSSION

A. Construction of a Series of Inhibitor Molecules from Hydroxychloroquine

After having done the modifications mentioned above, we managed to formulate 81 different molecules from Hydroxychloroquine with the help of the SeeSAR [16]. The main objective was to obtain a candidate molecule closer to Hydroxychloroquine but increase the receptor ACE2 (Table III).

TABLE III. RESULTS EXPLAINING THE FIXATION PROBABILITY OF EACH MOLECULE WITH THE RECEPTOR

Molecule	R1	R2	R3	R4	Fixation probability to the receptor site
Molecule_01	H	CH_3	CH_2	CH_2	YES
Molecule_02	H	CH_3	CH_2	O	YES
Molecule_03	H	CH_3	CH_2	CH-OH	YES
Molecule_04	H	CH_3	CH-NH_2	CH_2	YES
Molecule_05	H	CH_3	CH-NH_2	O	YES
Molecule_06	H	CH_3	CH-NH_2	CH-OH	YES
Molecule_07	H	CH_3	CH-CH_3	CH_2	YES
Molecule-08	H	CH_3	CH-CH_3	O	YES
Molecule_09	H	CH_3	CH-CH_3	CH-OH	YES
Molecule_10	H	CH_2-OH	CH_2	CH_2	YES
Molecule_11	H	CH_2-OH	CH_2	O	NO
Molecule_12	H	CH_2-OH	CH_2	CH-OH	NO
Molecule_13	H	CH_2-OH	CH-NH_2	CH_2	YES
Molecule_14	H	CH_2.OH	CH-NH_2	O	YES
Molecule_15	H	CH_2.OH	CH-NH_2	CH-OH	NO
Molecule_16	H	CH_2-OH	CH-CH_3	CH_2	YES
Molecule_17	H	CH_2-OH	CH-CH_3	O	YES
Molecule_18	H	CH_2-OH	CH-CH_3	CH-OH	YES
Molecule_19	H	CHO	CH_2	CH_2	NO
Molecule_20	H	CHO	CH_2	O	NO
Molecule_21	H	CHO	CH_2	CH-OH	NO
Molecule_22	H	CHO	CH-NH_2	CH_2	NO
Molecule_23	H	CHO	CH-NH_2	O	NO
Molecule_24	H	CHO	CH-NH_2	CH-OH	NO
Molecule_25	H	CHO	CH-CH_3	CH_2	NO
Molecule_26	H	CHO	CH-CH_3	O	NO
Molecule_27	H	CHO	CH-CH_3	CH-OH	NO
Molecule_28	CH_3	CH_3	CH_2	CH_2	NO
Molecule_29	CH_3	CH_3	CH_2	O	NO
Molecule_30	CH_3	CH_3	CH_2	CH-OH	NO
Molecule_31	CH_3	CH_3	CH-NH_2	CH_2	NO
Molecule_32	CH_3	CH_3	CH-NH_2	O	NO
Molecule_33	CH_3	CH_3	CH-NH_2	CH-OH	NO

Molecule_34	CH_3	CH_3	CH-CH_3	CH_2	NO
Molecule_35	CH_3	CH_3	CH-CH_3	O	NO
Molecule_36	CH_3	CH_3	CH-CH_3	CH-OH	NO
Molecule_37	CH_3	CH_2-OH	CH_2	CH_2	NO
Molecule_38	CH_3	CH_2-OH	CH_2	O	NO
Molecule_39	CH_3	CH_2-OH	CH_2	CH-OH	NO
Molecule_40	CH_3	CH_2-OH	CH-NH_2	CH_2	YES
Molecule_41	CH_3	CH_2-OH	CH-NH_2	O	NO
Molecule_42	CH_3	CH_2-OH	CH-NH_2	CH-OH	NO
Molecule_43	CH_3	CH_2-OH	CH-CH_3	CH_2	NO
Molecule_44	CH_3	CH_2-OH	CH-CH_3	O	NO
Molecule_45	CH_3	CH_2-OH	CH-CH_3	CH-OH	NO
Molecule_46	CH_3	CHO	CH_2	CH_2	NO
Molecule_47	CH_3	CHO	CH_2	O	NO
Molecule_48	CH_3	CHO	CH_2	CH-OH	NO
Molecule_49	CH_3	CHO	CH-NH_2	CH_2	NO
Molecule_50	CH_3	CHO	CH-NH_2	O	NO
Molecule_51	CH_3	CHO	CH-NH_2	CH-OH	NO
Molecule_52	CH_3	CHO	CH-CH_3	CH_2	NO
Molecule_53	CH_3	CHO	CH-CH_3	O	NO
Molecule_54	CH_3	CHO	CH-CH_3	CH-OH	NO
Molecule_55	F	CH_3	CH_2	CH_2	NO
Molecule_56	F	CH_3	CH_2	O	NO
Molecule_57	F	CH_3	CH_2	CH-OH	NO
Molecule_58	F	CH_3	CH-NH_2	CH_2	NO
Molecule_59	F	CH_3	CH-NH_2	O	NO
Molecule_60	F	CH_3	CH-NH_2	CH-OH	NO
Molecule_61	F	CH_3	CH-CH_3	CH_2	NO
Molecule_62	F	CH_3	CH-CH_3	O	NO
Molecule_63	F	CH_3	CH-CH_3	CH-OH	NO
Molecule_64	F	CH_2-OH	CH_2	CH_2	NO
Molecule_65	F	CH_2-OH	CH_2	O	NO
Molecule_66	F	CH_2-OH	CH_2	CH-OH	NO
Molecule_67	F	CH_2-OH	CH-NH_2	CH_2	NO
Molecule_68	F	CH_2-OH	CH-NH_2	O	YES
Molecule_69	F	CH_2-OH	CH-NH_2	CH-OH	NO
Molecule_70	F	CH_2-OH	CH-CH_3	CH_2	NO
Molecule_71	F	CH_2-OH	CH-CH_3	O	NO
Molecule_72	F	CH_2-OH	CH-CH_3	CH-OH	NO
Molecule_73	F	CHO	CH_2	CH_2	YES
Molecule_74	F	CHO	CH_2	O	NO
Molecule_75	F	CHO	CH_2	CH-OH	NO
Molecule_76	F	CHO	CH-NH_2	CH_2	NO
Molecule_77	F	CHO	CH-NH_2	O	YES
Molecule_78	F	CHO	CH-NH_2	CH-OH	NO
Molecule_79	F	CHO	CH-CH_3	CH_2	NO
Molecule_80	F	CHO	CH-CH_3	O	NO
Molecule_81	F	CHO	CH-CH_3	CH-OH	NO

B. Affinity Study

Parameters that explain in detail the affinity of each molecule for the receptor site include:

LE: Refers to each atom's bond energy in a molecule toward the receptor. In other words, it refers to the ratio between ΔG (Gibbs energy) and the number of atoms other than hydrogen in a molecule. If the LE value is greater than 0.3, the molecule in question will have a greater probability of fixing itself to the receptor [17]. The corresponding mathematical equation is given by:

$$LE = (1.37 \times plC50)/HA \quad (1)$$

plC50 corresponds to the Ligand concentration occupying 50% of the receptor, and HA represents the number of atoms other than hydrogen (heavy atoms).

LLE: Refers to a parameter used in the conception of drugs that permits evaluating the potential energy of a chemical bond and its lipophilicity to deduce its drug-likeness [18]. For the Ligand-receptor interaction to be favorable, the LLE value should be greater than or equal to 5 [19]. The corresponding mathematical equation is given by:

$$LLE = plC50 - Log\ (P) \quad (2)$$

Every molecule was docked with the receptor ACE2 model to show the possibility of forming a stable complex. From 81 molecules, it was found that only 19 were proved to interact with the specified target favorably. A drug's capacity to interact with a receptor is directly linked to its affinity for the receptor [20]. The estimated affinity for the 19 candidate molecules was calculated, and the results are shown in Table IV. The results show that only 8 molecules are having a good affinity when compared with molecule_01 (Hydroxychloroquine).

TABLE IV. ESTIMATED AFFINITY VALUES FOR THE CANDIDATE MOLECULES

Molecules	Estimated affinity (nm)	Molecules	Estimated affinity (nm)
Molecule_01	**6202803**	Molecule_13	48012075
Molecule_02	10178356	Molecule_14	238783948
Molecule_03	21861750	Molecule_16	**4668615**
Molecule_04	47841687	Molecule_17	**3998199**
Molecule_05	61083910	Molecule_18	**645211**
Molecule_06	7882945	Molecule_40	454448307
Molecule_07	**4408448**	Molecule_68	477694848
Molecule_08	**4351693**	Molecule_73	**5716436**
Molecule_09	**720512**	Molecule_77	1016590889
Molecule_10	**2407812**		

C. Bioactivity Prediction

The selected 8 molecules were examined in Molinspiration Chemoinformatics software to know the preferred binding protein of each molecule [21]. The results of the bioactivity prediction are summarized in Table V. The symbol "XXXX" means that the molecule can interact with 4 types of protein, one of them being an enzyme inhibitor, the symbol "XXXXX" means that the molecule can interact with 5 types of protein, one of them being an enzyme inhibitor, and symbol "0" means that there is no particular interaction with any protein. Only 4 molecules can have the same activity as Hydroxychloroquine.

TABLE V. BIOACTIVITY PREDICTION OF THE CANDIDATE MOLECULES

Molecules	Predicted bioactivity
Molecule_01	0
Molecule_07	XXXX
Molecule_08	0
Molecule_09	XXXXX
Molecule_10	0
Molecule_16	0
Molecule_17	0
Molecule_18	XXXXX
Molecule_73	XXXXX

D. Study on the Protein-Ligand Complexes

Following the analysis of the candidate molecules by Molinspiration, bioactivity results and the molecules' properties proved that only 4 of the 19 molecules had the desired

properties (had the estimated affinity closer to that of Hydroxychloroquine). These are Molecule_07, Molecule_09, Molecule_18, and Molecule_73. Figure 1 shows the candidate molecules in interaction with the receptor ACE2 and energy values in kJ/mol calculated from desolvation and interaction energies. SeeSAR was used to study these complexes. Each sphere represents atoms in the molecule, and each atom interacts differently with the atoms of the receptor (Figure 1).

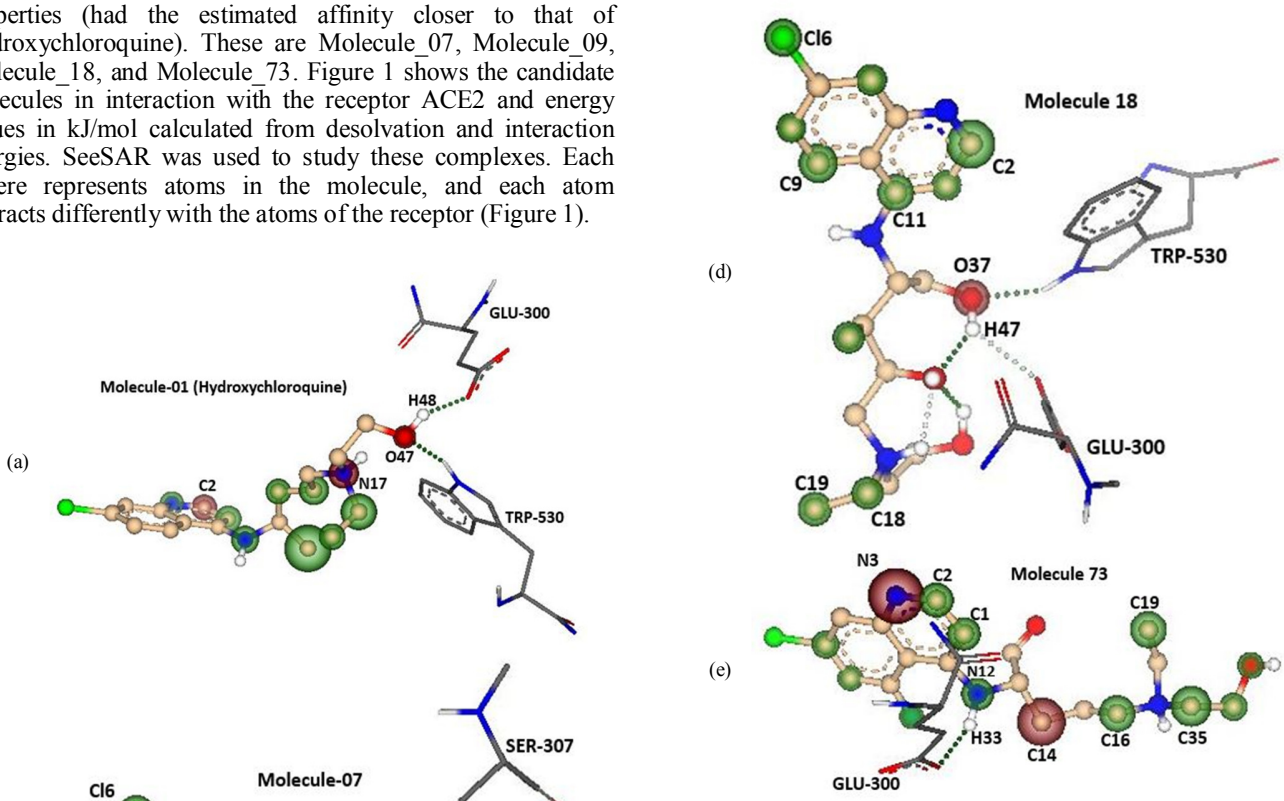


Fig. 1. Interaction of the 4 potential candidate molecules with the protein ACE2.

Each sphere represents an atom, and the greater the sphere's size, the greater the interaction with the receptor site. When the sphere is colored green, this signifies that the contribution of this atom is favorable. On the contrary, the sphere colored in red characterizes the unfavorable atom's interaction contribution. If the sphere is not colored, the value of ΔG is null or close to zero. Therefore, the contribution of the corresponding atom is negligible. Blue color represents polar regions, while yellow color represents hydrophobic regions [22]. The following points describe the interpretation of the results obtained in Figure 1.

- **Molecule 01**: The Hydroxychloroquine molecule shows a low affinity with its receptor site. Most of its atoms colored with green have a low ΔG values, and it has an unfavorable contribution formed by the N17 (2.7kJ/mol) and C2 (2.3kJ/mol).
- **Molecule 07**: atoms N17 and N3 are colored in red, with ΔG values of 9.3 and 1.6 kJ/mol, respectively. Therefore, the interaction with the receptor site is unfavorable. However, most of the atoms have negative ΔG values C19 (-5.7kJ/mol), O46 (-5.2kJ/mol), C18 (-3.7kJ/mol), C41 (-3.1kJ/mol), C10 (-2.9kJ/mol), and Cl6 (-1.9kJ/mol), signifying that their interaction with the receptor site is favorable.
- **Molecule 09**: C21 is the only atom colored in red (ΔG = 6.4kJ/mol), corresponding to unfavorable interaction. Atoms C47 (-3.7kJ/mol), C2 (-3.6kJ/mol), C19 (-

3.4kJ/mol), and O44 (-3.1kJ/mol), have negative ΔG values corresponding to favorable interactions with the ACE2 protein model.

- **Molecule 18**: Likewise, O37 has a positive ΔG value (2.3kJ/mol), so as a result, its interaction with the receptor site is unfavorable. For the atoms C2 (-4.2kJ/mol), C9 (-2.3kJ/mol), C11 (-2.0kJ/mol), Cl6 (-1.8kJ/mol), C19 (-1.6kJ/mol), and C18 (-1.2kJ/mol) the interaction with the receptor site is favorable.
- **Molecule 73**: For this molecule, N3 (7.0kJ/mol) and C14 (5.8kJ/mol) corresponding to unfavorable interaction. Atoms C35 (-4.1kJ/mol), C19 (-3.3kJ/mol), C16 (-3.2kJ/mol), C2 (-2.5kJ/mol), C1 (-2.3kJ/mol), and N12 (-2.3kJ/mol) have favorable interactions with ACE2.

After this analysis, we can conclude that Molecules 09 and 18 have the most significant probability to form a sufficiently stable complex with the receptor compared to the other molecules. However, for the other two molecules, the number of atoms with a favorable interaction with the receptor is very high compared to those having a non-favorable contribution, meaning that they also have sufficient capacity to interact with the receptor site.

The second step of docking is performed using SeeSAR software to determine the distances between the atoms of each candidate molecule with the amino acids of the protein receptor site (6M18). All the data are resumed in Table VI.

TABLE VI. DISTANCES BETWEEN ATOMS OF CANDIDATE MOLECULES WITH AMINO ACIDS OF THE RECEPTOR SITE (6M18)

Molecules	Atoms	Amino acids	Distances (A°)
Molecule-01	H48	Glu_{300}	1.84
	O47	Trp_{530}	2.01
Molecule-07	H47	Ser_{307}	1.93
Molecule-09	H45	Glu_{300}	1.94
	H53		2.05
	O44	Asn_{527}	1.96
	O51	Trp_{530}	1.88
Molecule-18	O37	Trp_{530}	2.01
	H47	Glu_{300}	2.25
Molecule-73	H33	Glu_{300}	1.95

- Molecule 1 (Hydroxychloroquine) forms 2 hydrogen bonds with the receptor site, the first is between H48 and Glu300 with a short distance and the second is between O47 and Trp530 with a moderate distance.
- Molecule 7 forms a single hydrogen bond with the receptor site, between H47 and Ser307 with a moderate distance.
- Molecule 9 forms 2 hydrogen bonds with Glu300, the first with H45 (short) and the second with H53 (moderate), ASN-527 forms another hydrogen bond (moderate) with O44. The littlest interaction was created between O51 and Trp530.
- Molecule 73 forms a single hydrogen bond with the receptor site between H33 and Glu300 with a moderate distance.

From these results, it can be concluded that Molecule 9 will have the best interaction with the receptor site.

E. Prediction of Electronic Properties by COSMO-RS

Conductor-like Screening Model for Real Solvents (COSMO-RS) is a quantum chemistry method based on thermodynamics, which helps to determine chemical potentials for solutions [23]. This method can predict sigma charge densities as well as chemical potentials for each species in the solution. The calculation is done in two main steps: Firstly, geometrical optimization on the molecule was done with the module Dmol3 [24] of the software BIOVIA Material Studio 2017 [25]. Secondly, the obtained cosmo-files were used to calculate sigma profiles and sigma potentials with the COSMOtherm software [26]. The sigma profile is divided into 3 distinct regions:

- HBD Region: Hydrogen bond donor region: the sigma values are less than -0.01eÅ^{-2}. The negative sigma values mean positive polarities [27].
- Non-Polar Region: σ values are given in the interval -0.01eÅ^{-2} to +0.01eÅ^{-2} [28].
- HBA Region: Hydrogen bond acceptor region: the σ values are greater than 0.01eÅ^{-2}. Positive sigma values represent negative polarities [29].

Figure 2 shows that the highest picks for all the selected molecules are found in the non-polar region. They are showing the tremendous non-polar character of the molecule surfaces. That said, the 5 molecules have net peaks in the HBD and HBA regions, making hydrogen bonds as acceptors and donors with the ACE2. The selected molecules meet the criteria that a candidate-molecule must possess to interact with the protein target: HBA, HBD, and hydrophobic sites [30].

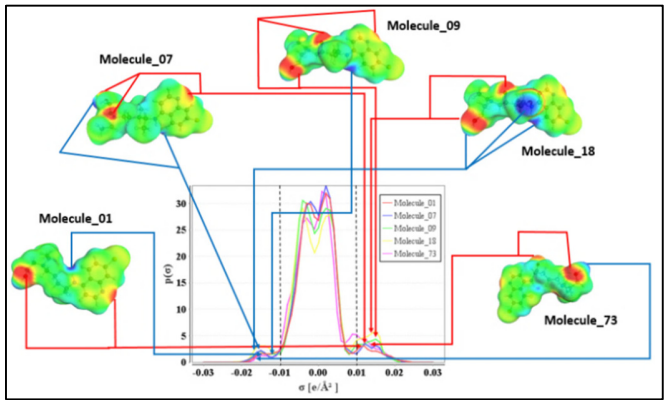


Fig. 2. Electronic charge densities of the candidate molecules.

Molecule 01 (Hydroxychloroquine) possesses a small HBD and HBA region. Molecule 07 shows a small HBD region and also some HBA regions. In Molecule 09, there are 3 regions capable of accepting hydrogen atoms and a small hydrogen donor region. Molecule 18 possesses a large enough hydrogen donor region as well as a hydrogen bond acceptor region. A tiny region in Molecule 73, almost negligible, can donate a hydrogen atom (colored in blue) while a more significant part,

colored in red, represents the hydrogen acceptor region; The most prominent picks in the range $-0.01eÅ^{-2}<\sigma<+0.01eÅ^{-2}$ are due to the non-polar chemical groups such as CH3, CH2, CH, which are more abundant in the molecules. Negatively charged atoms such as O^- constitute hydrogen acceptors (region HBA) [31]. The positively charged atoms or atoms with lone pairs of electrons are responsible for the picks in the region HBD (NH, NH2, and NH3). Figure 3 proves the results obtained from the sigma profiles and the energies of desolvation and interaction. All candidate molecules have strong affinities HBD and HBA well balanced. This demonstrates that they have sufficient solubility in water and blood after administration [28].

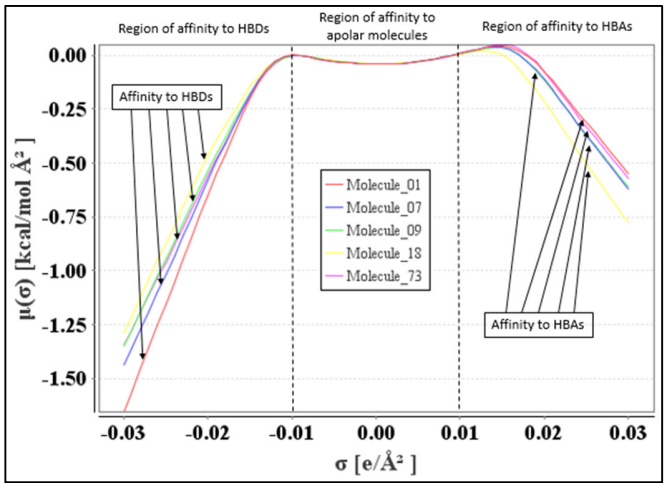


Fig. 3. Sigma potentials of the four candidate molecules.

IV. CONCLUSION

Taking hydroxychloroquine as the primary molecule, we built 81 new derivative molecules, of which only 4 molecules had improved affinity for ACE2. The modifications of the hydroxychloroquine structure at critical positions enhance properties such as affinity for the receptor site, solubility, and permeability and allow reconsidering the hydroxychloroquine derivative molecules for therapeutic use as a ligand for ACE2. Nevertheless, in-vitro and in-vivo studies will help confirm the results obtained in this study.

ACKNOWLEDGMENT

The authors would like to express their gratitude and acknowledge the support of Ferhat Abbas Setif-1 University and the DGRSDT (La Direction Générale de la Recherche Scientifique et du Développement Technologique).

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